CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

REMARKS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

At the outset, Applicants wish to address the showing required by 37 CFR § 1.116(b) as to why this amendment is necessary and was not presented earlier. This amendment is in-part responsive to new points made by the Examiner for the first time in the final rejection, specifically the Examiner's comments about Applicants' use of the open-ended terminology "comprising" and her reference to MPEP § 2111.03. Accordingly, this amendment is necessary. Further, since this is the first substantive response to the final rejection, this amendment could not have been presented earlier. Beyond that, Applicants note that this amendment in the remainder only cancels claims, i.e., claims 35 and 36, and, thus, does not, beyond Applicants' reply to the Examiner's new points, raise any other issues that would require anything more than a cursory review by the Examiner.

The sole remaining issue is the rejection of claims 9, 11, 29, 30 and 35 under 35 USC § 102 (a and e) as being anticipated by Barrat et al. ("Barrat"), US 2002/0090357, as evidenced by Fujimaki et al. ("Fujimaki"), *Clin. Develop. Immunol.,* pp. 1-12 (2008). In response, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

The Examiner states that "the '357 publication teaches that vitamin D3 and dexamethasone are immunosuppressive agents (see page 2), and are not considered to be an 'activation stimulus' as recited in the instant claims. Furthermore, …the instant claims

are drawn to a method for producing regulatory T cells which 'comprises' activating $CD4^+$ $CD25^+$ T cells.... * * * Thus, the instant claims are open to additional unrecited steps or elements. The '357 publication teaches a method of producing regulatory T cells comprising contacting unactivated CD4+ CD25+ T cells with an immunosuppressive agent and an activation stimulus consisting of plate-bound anti-CD3 and soluble anti-CD28, which reads on the instant claims."

Claim 9 (and thus also the other pending claims, which depend from or incorporate the limitations of claim 9) has been amended for clarification to specify that the anergic state inducing agent consists of $CD4^+$ $CD25^+$ T cells. Anergy, or lack of proliferation in response to certain stimuli, is a well-known property in the art and is explained, for example, in paragraph 0003 of the published application. Support for the amendments to the claims can be found, for example, in paragraph 0011 of the published application, which states that the invention provides a method for producing Tr1-like regulatory T cells comprising "contacting the $CD4^+$ $CD25^-$ T cells with an anergic state inducing agent *ex vivo*....", and in paragraph 0009, which explains that preferably the $CD4^+$ $CD25^-$ T cells are anergized by contact with $CD4^+$ $CD25^+$ T cells.

Applicants respectfully submit that these amendments clearly distinguish the instant claims from the cited combination of references. The Examiner says "[t]he use of 'consisting of' in the body of the claims does not limit the open-ended 'comprising' language of the claims (see MPEP 2111.03). Thus, the instant claims are open to additional unrecited steps or elements." In response, Applicants respectfully submit that the Examiner is not completely correct. MPEP § 2111.03 makes perfectly clear that:

> "When the phrase 'consists of' appears in a clause of the body of a claim, rather than immediately following the preamble, ***it limits*** * * * ***the element set forth in that clause;*** other elements are not excluded from the claim as a whole (emphasis added)."

In the present case, claim 9 says the "activation stimulus [consists] of: (a) plate-bound anti-CD3 and soluble anti-CD28 antibodies; or (b) mature dendritic cells; and the $CD4^+$ $CD25^-$ T cells are anergized "by contacting the $CD4^+$ $CD25^-$ T cells *ex vivo* with an anergic state inducing agent consisting of said activated $CD4^+$ $CD25^+$ T cells to yield human Tr1-like regulatory cells."

In view of MPEP § 2111.03, and Applicants' use of "consisting of" language, these elements of claim 9 are strictly limited to the recited elements. The fact that the open-ended terminology "comprising" is used immediately following the preamble does not, in fact, open up these two elements to either an activitation stimulus having other ingredients besides those listed after "consisting of" or to an anergic state inducing agent having other ingredients than those listed after "consisting of."

Applicants respectfully submit that the cited combination of references does not teach or suggest any embodiments meeting the terms of the instant claims as properly construed.

In contrast to the amended claims, the '357 publication teaches methods for making regulatory T cell populations that require "contacting a naïve T cells *[sic]* with a stimulatory signal and an appropriate amount of a combination of Vitamin D3 and Dexamethasone, wherein the contacting results in differentiation to a regulatory T cell" ('357 paragraph 0007). The '357 publication teaches that vitamin D3 and dexamethasone

are immunosuppressive agents, as acknowledged in the Office Action (page 3, third full paragraph); see '357 paragraph 0021)). Accordingly, the '357 publication does not anticipate the amended claims and this rejection of the claims should be withdrawn.

Another important difference between the claimed methods and those taught in the '357 publication is that the cells produced by the methods are different, as evidenced by their different properties such as cytokine production. The '357 authors characterize their resulting cells: "Type 1 T-regulatory (Tr1) cells are defined, in part, by their unique cytokine profile: they produce high levels of IL-10, significant levels of TGF-β, IL-5, and IFN-γ, but no significant amounts of IL-4 or IL-2" ('357 paragraph 0020). Further, the '357 authors also indicate that the disclosed methods and resulting cells are similar to those obtained by addition of exogenous IL-10, as taught by Groux *et al.* (1997) *Nature* 389: 737-742 (see '357 at paragraph 0018), which are similarly described by those authors as Tr1 cells.

This contrasts with the cells of the present invention, which the present application distinguishes from Tr1 cells (see, *e.g.*, publication paragraph 0041 on page 4, left column). Specifically, the present application teaches (at paragraph 0041, page 4, left column) that:

> "CD4+ T cells with low proliferative capacity, that are generated in the presence of [exogenous] IL-10 results in a state of functional responsiveness without death, termed anergy (Iellem et al., *J. Exp. Med.* 194: 847-853 (2001)). CD4+ T cells with low proliferative capacity, that are generated in the presence of [exogenous] IL-10 have been termed type 1 T regulatory cells (Tr1). The cells [as described in the present application] that are generated in the

> presence of CD4+ CD25+ T cells show some characteristics resembling Tr1 cells, especially their low proliferative capacity and the high level production of IL-10. But in some instances they differ, as Tr1 are also defined by their ability to produce TGF-β and anergized CD4+ CD25- T cells did not produce significant amounts of TGF-β at least by the assay used."

Indeed, the present application teaches that although IL-10 is secreted to some extent by $CD4^+$ $CD25^+$ T cells and at higher levels by anergized $CD4^+$ $CD25^-$ T cells, $CD4^+$ $CD25^+$ T cells can induce anergy in $CD4^+$ $CD25^-$ T cells in the absence of exogenously added IL-10 or other exogenous immunosuppressive agents; rather, cell contact was shown to be important for inducing anergy (see, *e.g.*, published application at page 3 (paragraph 0040), right column).

In view of the foregoing, Applicants respectfully submit that the method of the present claims is distinguished from Barrat's method and, therefore, Barrat does not anticipate the present claims, even as evidenced by Fujimaki. An early notice to that effect is earnestly solicted.

Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700

so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,

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